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Renal Carcinoid and Horseshoe Kidney: A Frequent Association of Two Rare Entities—A Case Report and Review of the Literature

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We report the case of a primary renal carcinoid tumor associated with a horseshoe malformation in a 43-year-old man who presented with testicular pain. The tumor was centrally located and purely solid and had features ascribed to hindgut neuroendocrine neoplasia. The relative risk of developing a carcinoid tumor in a horseshoe kidney is estimated to be ×82.

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KEY WORDS: **kidney; carcinoid tumor; horseshoe kidney; neuroendocrine; hindgut; relative risk**

INTRODUCTION

Primary carcinoid tumor of the kidney is a very rare neoplasm. In the literature, 39 cases have been reported so far [1–39], including five cases that were reported twice [2,3,6–9,19,20,27,28]. Among these, seven tumors arose in a horseshoe kidney [6,7,15,30,33,34,38,39], one case having been published twice [6,7]. In other organs, carcinoid tumor is generally believed to derive from in-

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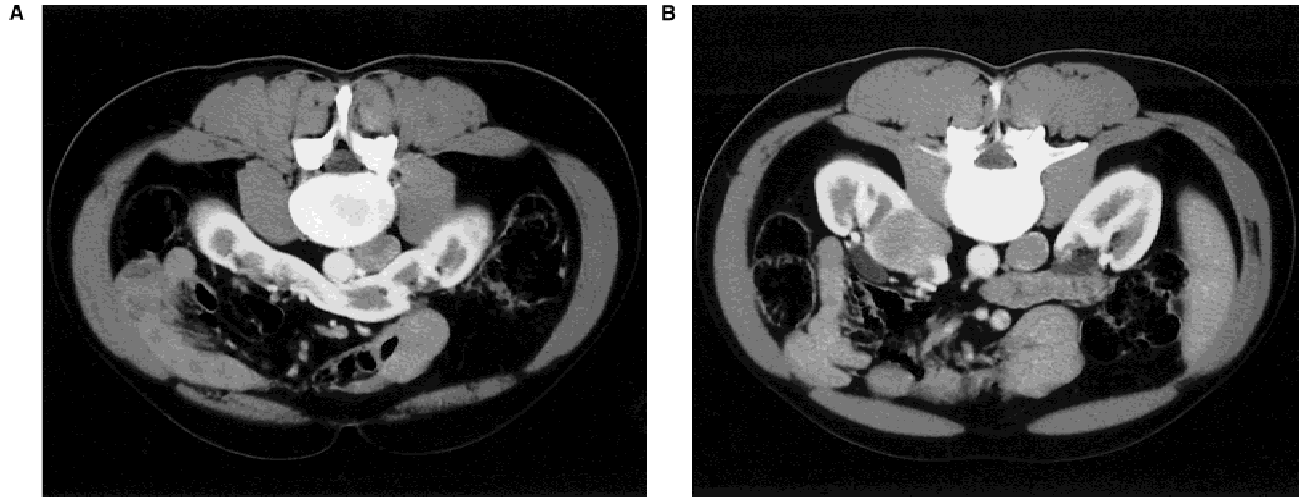

Fig. 1. CT scan showing horseshoe kidney **(A)** with superimposed well-circumscribed, homogeneous and solid mass **(B)** in the left region, medial to the isthmus.

Fig. 2. Bisected portion of horseshoe kidney revealing a centrally positioned carcinoid tumor bulging in the hilar region. Note the circumscribed contour and the lobulated, solid homogeneous cut surface.

trinsic neuroendocrine cells (designated endocrine-paracrine cells or amine precursor uptake and decarboxylation [APUD] cells) or to arise in the setting of teratomatous (germ cell) neoplasia as an emerging neuroendocrine tumor component. As neuroendocrine cells have not yet been identified in the normal kidney, and its association with an intrarenal indisputable teratomatous component is extremely rare [6,38], the histogenesis of renal carcinoid is still disputed. We hereby report the eighth case of primary renal carcinoid in association with a horseshoe kidney malformation.

CASE REPORT

In May 1996, a 43-year-old man presented with left testicular pain of 3 months' duration, without any associated paraneoplastic manifestation. His previous medical history was otherwise unremarkable. Imaging studies, including abdominal ultrasound and computed tomography (CT), revealed a horseshoe kidney (Fig. 1A) with a superimposed 3.5-cm solid, circumscribed tumor located in the left medial aspect close to the isthmus (Fig. 1B). Chest radiography and bone scan were negative. The blood cell count and serum biochemical profile were within normal limits. A left radical nephrectomy including the isthmus was performed, the kidney being supplied with three arteries and four veins. The postoperative course was uneventful, and no elevation of serum 5-hydroxyindolacetic acid was observed. There was no evidence of disease at 20 months follow-up.

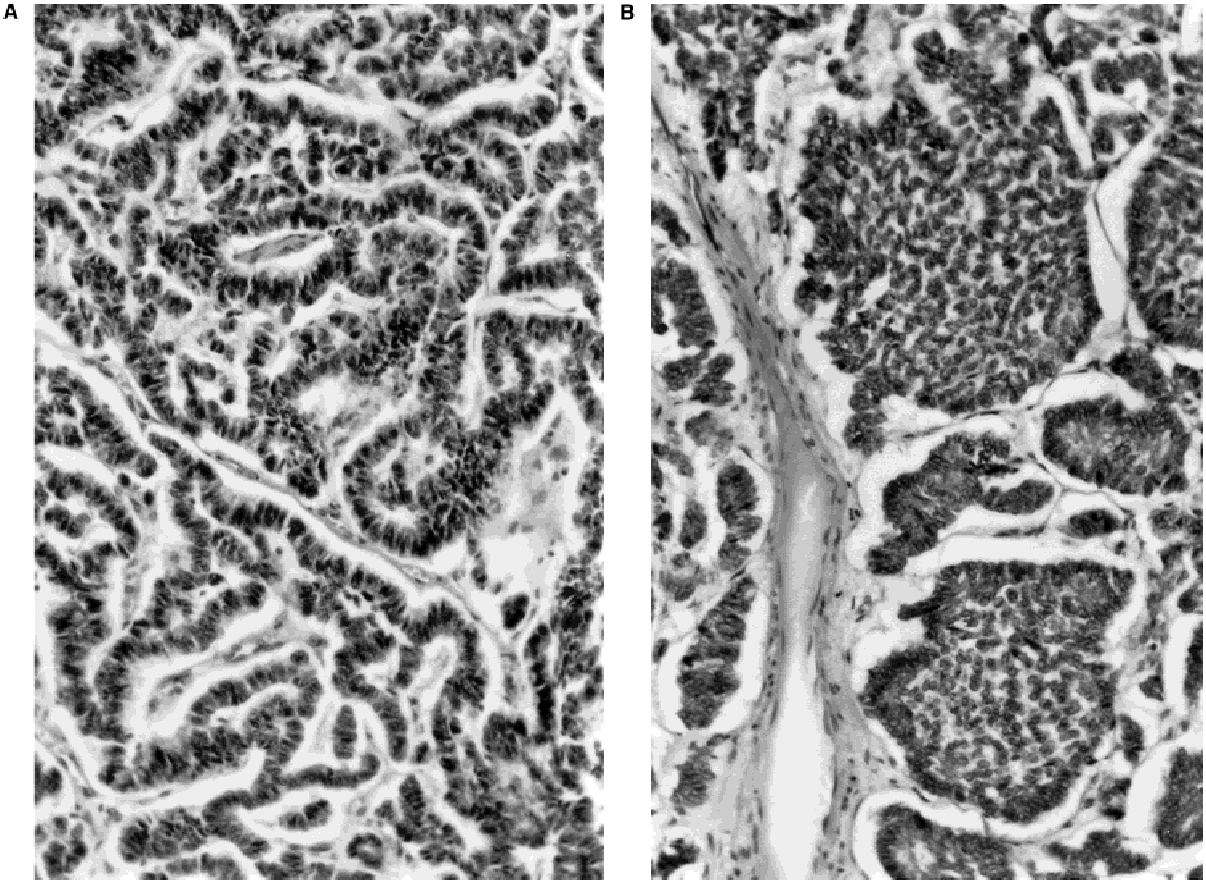

Fig. 3. Renal carcinoid composed of monotonous tumor cells with trabecular **(A)** and insular **(B)** patterns (H&E, ×100).

MATERIALS AND METHODS

The specimen was fixed in 10% buffered formaldehyde; tumor samples were also fixed in B5 and alcohol. Sections were stained with hematoxylin and eosin (H&E), and periodic acid-Schiff (PAS) with/without α-amylase. For immunohistochemical analysis, the streptavidin-biotin-peroxidase complex method with selective use of protease was used for the following antibodies: CAM 5.2 (Becton Dickinson, Mississauga, Ontario, Canada; dilution 1:80), cytokeratin AE1/AE3 (Boehringer Mannheim, Indianapolis, IN; dilution 1:800), epithelial membrane antigen (EMA) (Dakopatts, Mississauga, Ontario; dilution 1:100), vimentin (Dakopatts; dilution 1: 80; alcohol-fixed tissue), prostate-specific antigen (PSA)(Dakopatts; dilution 1:500), prostatic acid phosphatase (Sigma Chemical Co., St. Louis, MO; dilution 1:8,000), chromogranin A (Boehringer Mannheim; dilution 1:3200), synaptophysin (Dakopatts; dilution 1: 100), CD 57/Leu 7 (HNK-1) (Novo Castra Laboratories, Newcastle upon Tyne, UK; dilution 1:50), serotonin (Zymed Laboratories, South San Francisco, CA; dilution 1:400), calcitonin (Zymed Laboratories; undiluted) and somatostatin (Zymed Laboratories; undiluted). All tissue blocks (total of 17, including 15 with a tumor component) were stained at least for basic neuroendocrine markers (chromogranin and synaptophysin). For ultrastructure, glutaraldehyde-fixed tumor was embedded in Epon, and thin sections were stained with uranyl acetate and lead citrate.

PATHOLOGIC FINDINGS

The partial nephrectomy specimen (after removal of perinephric fat) weighed 221 g and measured 14.5 × 6.5 × 3.5 cm. In the mid-, central, and paraisthmic aspect of kidney, there was a well-circumscribed, boomerang-shaped, bulging and lobulated tumor, which measured 7 × 3.5 × 3.2 cm. The tumor was entirely surrounded by peritoneum-like membranous tissue on the hilar aspect, whereas it was located at 0.7 cm from the surgical resection margin. On cut surface, the tumor was bulging and had a homogeneous, solid and soft, yellow appearance without hemorrhage or necrosis (Fig. 2). The adjacent renal parenchyma appeared normal. No hilar lymph node was identified.

Microscopically, the tumor included trabecular (gyriform) (Fig. 3A) and insular (nesting) (Fig. 3B) patterns; it was composed of monotonous cells with an ill-defined outline and eosinophilic granular cytoplasm. The nuclei had a round contour and a delicate stippled chromatin pattern with occasional small indistinct nucleoli. Mitotic activity and necrosis were absent. There was a delicate fibrovascular framework, whereas some areas showed marked fibrous desmoplasia with entrapped/attenuated tumor cells (Fig. 4). Some tumor areas were punctuated with microcystic spaces measuring up to 1.3 mm, often containing eosinophilic and PAS-diastase-resistant proteinaceous material. The tumor/parenchymal interface was characterized by an abrupt transition or the interposition of a fibromuscular thick capsule, including entrapped neoplastic elements or residual renal tubules. The pyelocalyceal and ureteral urothelium was normal.

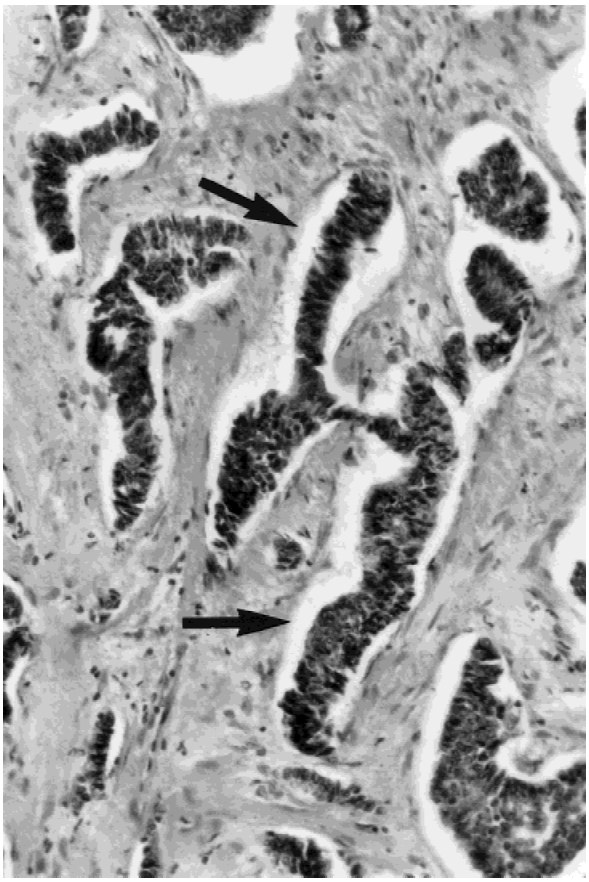

Fig. 4. Renal carcinoid including areas of marked fibrous desmoplasia with entrapped and attenuated clusters of tumor cells (arrows) (H&E, ×100).

Tumor cells showed cytoplasmic coexpression of CAM 5.2 (diffuse), vimentin (regional; alcohol fixation), synaptophysin (diffuse; formalin and B5 fixation) (Fig. 5A) and CD 57/Leu 7 (regional, predominant punctuated pattern; B5 fixation) (Fig. 5B). Diffuse and weak cytoplasmic immunoreactivity for prostatic acid phosphatase was observed. Rare, isolated tumor cells were strongly immunoreactive for chromogranin A and serotonin. Cells were otherwise negative for cytokeratin AE1/AE3, EMA, PSA, calcitonin, and somatostatin. No immunoreactive neuroendocrine cell was detected in the non-neoplastic renal parenchyma and renal pelvis/hilum.

Ultrastructure revealed groups of cohesive, polygonal tumor cells united by junctional complexes and with an intervening delicate capillary framework. A large number of cells contained neurosecretory-type, membrane-bound, round granules of varying density and ranging

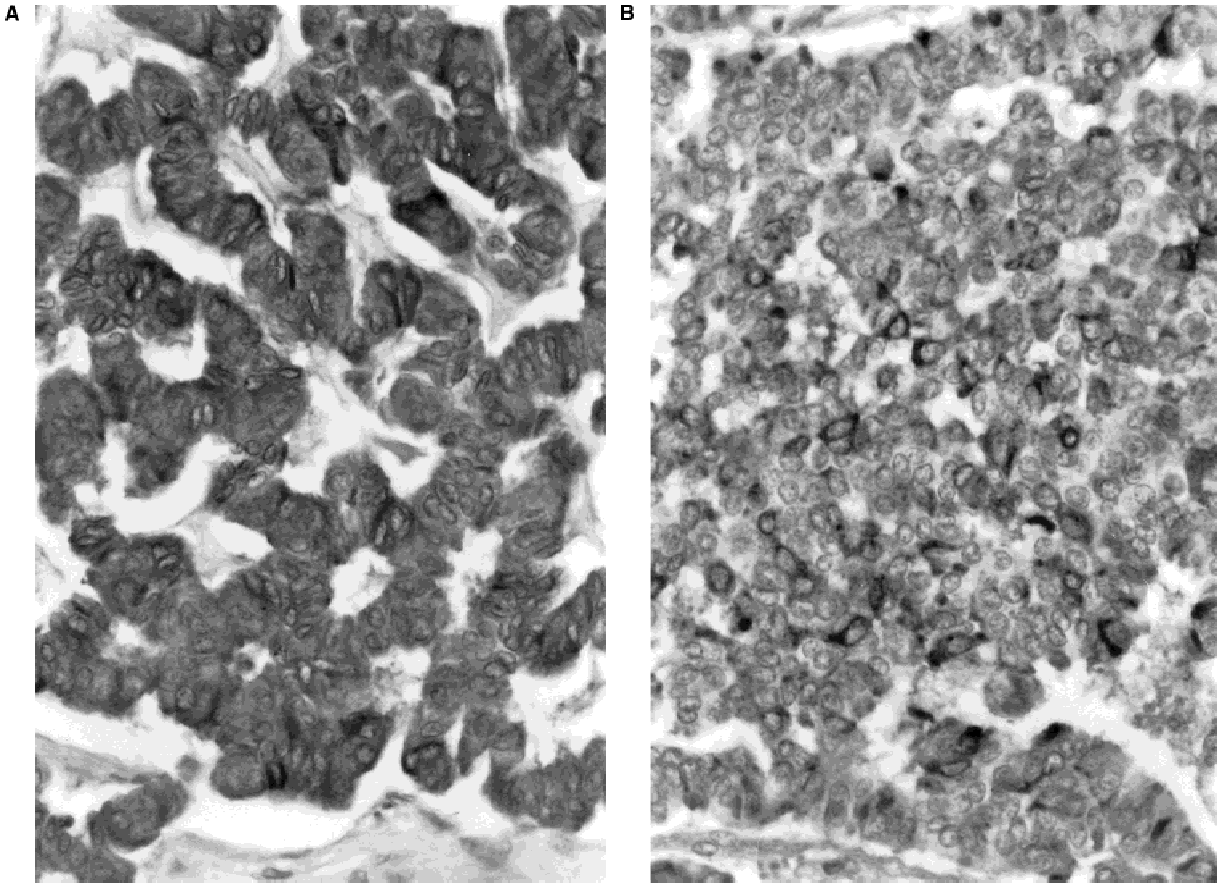

Fig. 5. Renal carcinoid tumor cells showing strong cytoplasmic coexpression of synaptophysin **(A)** and CD57/Leu 7 (punctuated pattern) **(B),** characteristic of a neuroendocrine phenotype (immunostaining, ×250).

about 100–300 nm in diameter. Otherwise the cytoplasm frequently contained parallel or circular arrays of rough endoplasmic reticulum. The nuclei were frequently notched with margination of heterochromatin.

DISCUSSION

Since the first description of a primary renal carcinoid tumor in 1966 by Resnick et al. [1], only 39 cases of this exceedingly rare neoplasm have been reported in the literature[1–39]. Furthermore, five of these cases were published twice [2,3,6–9,19,20,27,28]. Among the 40 cases documented so far, including the present report, eight (20%) arose in a horseshoe kidney (Table I). Krishnan et al. [38] calculated a relative risk of ×62 for the occurrence of renal carcinoid in association with a horseshoe kidney. Their risk estimation was based on 32 documented cases of renal carcinoid, including five tumors in a horseshoe kidney. On the basis of our current review of the literature (and including the present case), we estimated the relative risk for such association to be ×82. We calculated this risk using a high estimate of 1/400 for the incidence of horseshoe kidney in the general population, similar to Krishnan et al. [38].

Among the eight patients with documented carcinoid tumor within a horseshoe kidney, there were four women and four men whose ages ranged from 23 to 79 years (average 50.5 years) (Table II). Most common presenting symptoms were abdominal and flank pain, similar to carcinoid tumor arising in a normal kidney. No patient had a paraneoplastic manifestation related to the carcinoid syndrome. The tumor epicenter was located in the isthmus in three cases [33,34,38], and paraisthmic in the present case. A cystic component lined with an urothelial and/or mucinous goblet cell lining (with few interspersed, basally positioned neuroendocrine cells) was observed in three specimens [6,30,38], one of which was also including a dysplastic renal component [6]. Whether this cystic component was of neoplastic teratomatous nature or represented an entrapped calyceal structure with secondary intestinal metaplasia is arguable, although the latter view is currently favored [38].

Although the small number of reported cases precludes prognostic determination, tumors that arose in a horseshoe kidney appeared to be less aggressive than those involving a normal kidney. No evidence of renal vein/extrarenal invasion was documented, whereas only one patient developed liver metastases at 2 years follow-up [34].

TABLE I. Reported Cases of Primary Carcinoid Tumor in Horseshoe Kidney*

Source/year [Ref.]	Sex/Age	Clinical presentation	Gross	Extrarenal invasion	Metastasis de novo	Demonstration of tissue hormone	Outcome
Fetissof et al., 1984 [6] Lanson et al., 1978[a] [7]	M/65	Fever, flank mass	2-cm tumor nodule arising within cystic teratoma (''dysplastic'' horseshoe kidney)	No	No	Glucagon, serotonin, somatostatin	No follow-up
Acconcia et al., 1988 [15]	F/29	Hypogastric pain, hematuria	10 × 7-cm, circumscribed, lower pole	No	No	No	ANED at 36 mo
Machet et al., 1994 [30]	F/79	Abdominal pain	6 cm, cystic	No	No	Serotonin, somatostatin	ANED at 36 mo
Van den Berg et al., 1995 [33]	F/55	Atypical chest pain	5 cm, circumscribed, isthmus	No	No	Pancreatic polypeptide	ANED at 36 mo
Kurl et al., 1996 [34]	F/62	Flank pain	9 × 5 × 5-cm, isthmus, cystic component	No	No	Pancreatic polypeptide, glucagon, serotonin	AWD, liver metastasis at 24 mo
Krishnan et al., 1997 [38]	M/48	Pyelonephritis	6 × 5 × 2.5 cm, isthmus, cystic component	No	No	Glucagon, pancreatic polypeptide, VIP, serotonin, somatostatin	ANED at 24 mo
Lodding et al., 1997 [39]	M/23	Abdominal pain	2 cm^3, circumscribed	No	No	Not done	ANED at 36 mo
Present case	M/43	Testicular pain	7 × 3.5 × 3.2 cm, circumscribed	No	No	No	ANED at 20 mo

*ANED, alive, no evidence of disease; AWD, alive with disease; VIP, vasoactive intestinal polypeptide.
[a]Same case as reported by above author.

TABLE II. Comparison Between Carcinoid Tumor in Horseshoe and Normal Kidney

	No. of patients	Female/Male	Average age (range, yr)	Extrarenal invasion	Metastatic de novo	Dead from disease
Renal carcinoid in horseshoe kidney	8	4/4	50.5 (23–79)	0	0	0
Renal carcinoid in normal kidney	32	16/16	47.9 (13–67)	7	9	3

Originally recognized in a carcinoid tumor involving a normal kidney [25], cellular expression (detected by immunohistochemical staining) of prostatic acid phosphatase has been documented in three subsequent cases, including the present report [28,29,37]. Expression of prostatic acid phosphatase has been commonly observed in rectal carcinoid tumor of hindgut derivation, whereas it is virtually absent in tumors of foregut and midgut derivation [40,41]. Furthermore, the combined trabecular/insular architectural pattern of renal carcinoid and the tissue hormonal profile (secretion of glucagon, pancreatic polypeptide, and/or somatostatin) [2,6,10,22,24,27,29,30,33,34,38] previously observed in many such tumors are in keeping with neuroendocrine neoplasia of hindgut derivation [42,43].

As no intrinsic neuroendocrine cell has been identified so far within the normal kidney, four hypotheses have been postulated regarding the pathogenesis of renal carcinoid: (1) it would derive from a primitive/stem cell undergoing neuroendocrine differentiation through neoplastic activation of gene sequences common to neuroendocrine-programmed cells [44]; (2) it would derive from misplaced or entrapped neural crest tissue (APUD cells) in the hilar (central) aspect of kidney during embryogenesis [12]; (3) it would derive from interspersed neuroendocrine cells associated with intestinal metaplasia of the pyelocalyceal urothelium (e.g., induced by chronic infection) [12,38]; and (4) it would arise within teratoma as a major emerging neuroendocrine component, hence a reflection of germ cell neoplasia. In the present case, there was no morphological evidence sustaining the last two hypotheses.

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